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## CONDITIONAL PETITION FOR EXTENSION OF TIME

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## REMARKS

Claims 24-38 are pending in the application. The claims have been rejected under various statutory provisions. The rejections will be addressed in the sequence in which they were presented in the office action.

New claims 39-42 have been added and are fully supported. The new claims do not introduce new matter. The claims add limitations that further distinguish the method from Sanchez.

### RESPONSE TO EXAMINER'S REMARKS

Examiner's states that the mechanism of action of a treatment has no bearing on the patentability of the claims. This conclusion is logical only if the reference inherently teaches the process or method -- inhibition of sebum production.

The attached exhibit indicates that permeability of active agents through the skin, is dependent on the vehicle and that "the choice of vehicle may be as important as the active drug." See Exhibit, p.4, "*Vehicle.*"

Most important, the lipophilic nature of the vehicle favors penetration through the stratum corneum, which is a necessary step to reaching the sebaceous glands to affect sebum production. Exhibit, p. 3, col. 2. The lipophilic nature of the composition also results in hydrating the skin by preventing transepidermal water loss. Exhibit, p. 4, *Hydration.*

In light of this background, people of ordinary skill in the art would not extract from Sanchez's disclosure of "substantially oil-free" compositions, that his compositions would inherently permeate the skin and affect the production of the sebaceous glands.

Therefore, Sanchez's concept is quite different than Applicants' which employs an oily phase to provide these benefits, as well as being a vehicle for the cyclodextrin.

ANTICIPATION

Examiner asserts that claims 24-26 and 28-29 are anticipated by US 5, 296,472 to Sanchez, et al. Claim 27 is not deemed anticipated.

New claim 40 incorporates the subject matter of claim 27 into claim 24. In accordance with the office action, it is believed that claim 40 is not anticipated.

OBVIOUSNESS

Claims 30-38 are rejected for allegedly being obvious over Sanchez. Specifically, Examiner believes that Sanchez's disclosure at col. 5, lines 12-20 are sufficient to render the claims obvious.

It is first indicated that Sanchez sets an upper limit of 10% detergents, organic solvents, oils, waxes, latexes and other lipid-type agents. This is not an unqualified teaching of an oily phase. In fact, Sanchez's concept requires that any of his compositions be "substantially oil-free" because the cyclodextrin's capacity to further complex with lipid would, in Sanchez's view, be saturated even before application to the skin.

Therefore, Sanchez would not be viewed as suggesting compositions that would affect the substrata of the epidermis. In fact, every indication in Sanchez is that his preparations are for delipidation and nothing more.

For this reason, the rejections should be withdrawn

SANCHEZ DOES NOT PROVIDE AN ENABLING DISCLOSURE

It is well established that a proper reference under 35 USC §§102 or 103 must be enabling in the sense of 35 USC §112, ¶1. It is suggested that the Sanchez reference is not enabling to that extent. Pertinent is the following quote from *In re Le Grice*, 133 USPQ 365, 374 (CCPA 1962):

> "[T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains ***could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention*** on which a patent is sought. [Emphasis added.]"

See also, *In re Hoeksema,* 158 USPQ 596, 601 (CCPA 1968), wherein the Court stated:

> "While *In re Le Grice* was bottomed on an issue arising under 35 U.S.C. 102 where the reference was a 'printed publication,' that test, in our view, is also properly applicable to issues arising under 35 U.S.C. 103."

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. MPEP § 2164.01

In view of the state of the art as explained in the Exhibit, and Sanchez's explicit requirement for substantially oil-free compositions, it is not clear how Sanchez could render claims 30-38 obvious.

There are neither exampl s nor a recitati n of specific oil components that would negate Sanchez's clear aversion to oily compositions. Examiner has not provided any reference having cyclodextrins in oily compositions -- thus, it does not follow that it would be obvious to persons in the art that any combination of components would suffice.

For this reason, the rejections of claims 30-38 should be withdrawn.

## CONCLUSIONS

Applicants respectfully point out that Examiner's rejections have been addressed so as to overcome the rejections.

Respectfully Submitted,

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EXHIBIT

# GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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CHAPTER 64

# DERMATOLOGICAL PHARMACOLOGY

*Cynthia A. Guzzo, Gerald S. Lazarus, and Victoria P. Werth*

*The skin has many essential functions, including protection, thermoregulation, immune responsiveness, biochemical synthesis, sensory detection, and social and sexual communication. Therapy to correct dysfunction in any of these activities may be delivered systemically, intralesionally, topically, and through ultraviolet radiation. Topical therapy is a convenient method of treatment, but its efficacy depends on understanding the barrier function of the skin, primarily within the stratum corneum.*

*Corticosteroids and retinoids are important systemic and topical therapeutic agents for skin disease. Oral steroids are employed in high doses to treat very serious cutaneous eruptions. Fortunately, over the years, structural modification of the hydrocortisone molecule has produced compounds of increased potency that can now be used topically to treat many dermatological diseases. Powerful retinoids, including isotretinoin for treatment of acne and etretinate for psoriasis, are administered orally; modification of these molecules has resulted in topical agents that are being explored for their anticarcinogenic and antiaging effects.*

*Antibacterial, antiviral, and antifungal agents are employed widely both topically and systemically. Oral antimalarial, chemotherapeutic, and immunosuppressive agents, dapsone, and antihistamines frequently are used for treatment of dermatological diseases. Calcipotriene, a vitamin D analog, and anthralin are major topical agents for psoriasis. Ultraviolet radiation therapy is a frequent mode of treatment for psoriasis and can now be administered independently or in combination with drugs such as psoralens or coal tar. However, ultraviolet radiation is itself responsible for the production of cutaneous cancers. The prophylactic use of sunscreens may reduce or prevent premalignant and malignant skin lesions induced by UV light, so their use is highly recommended. Numerous other compounds are employed in dermatological therapy, including minoxidil, which is the only agent approved for the treatment of pattern or androgenetic alopecia.*

*Finally, the accessibility of the skin holds great promise in the near future to correct cutaneous and systemic diseases using gene therapy.*

cosmetic industry sales in the United States are estimated to be about 20 billion dollars per year. Sales of dermatological pharmaceuticals came to approximately 4 billion dollars in 1993. These figures reflect the importance of appearance and cutaneous comfort in modern society. Dermatological pharmacology is unusual in several ways. Uses and indications for some dermatological pharmaceutical agents and cosmetic products overlap. Cutaneous therapeutic agents include sunscreens, moisturizers, and topical antiaging products. Dermatological therapeutic agents include ancient topical medications without a theoretical basis for action (*e.g.*, topical coal tar for psoriasis) and agents that have been developed using state-of-the-art structure/activity relationships and *in vitro* evaluation of absorption, transport, and metabolism (*e.g.*, isotretinoin for the treatment of acne).

A unique aspect of dermatological pharmacology is the accessibility of the skin for diagnosis and therapy. Therapeutic agents can reach epidermal keratinocytes as well as immune-competent cells in the skin that are involved in the pathogenesis of cutaneous diseases. Drugs used in treatment of skin diseases can be delivered systemically, applied topically, or injected directly into the dermis. An unusual form of treatment, phototherapy employing ultra-

violet radiation, can be administered alone or in combination with oral medication. An example of multimodal therapy of skin diseases is given in Figure 64–1, which shows that, in psoriasis, all of these therapeutic routes are used. The epidermal barrier and parameters controlling absorption through that barrier must be understood for effective use of topical drug delivery.

**The Skin as a Barrier.** The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. The barrier function is largely carried out by the epidermis, more specifically the outermost layer—the stratum corneum—as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin (Wepierre and Marty, 1979). The stratum corneum cells, corneocytes, are nonviable, having lost nuclei and cytoplasmic organelles. The cells are flattened, and fibrous proteins, or keratins, are aligned into disulfide cross-linked macrofibers, in association with filaggrin, which is the major protein component of the keratohyalin granule. Each cell develops a cornified envelope resulting from cross-linking of involucrin and keratohyalin. This constitutes the insoluble exoskeleton that acts as a rigid scaffold for the internal keratin filaments. The intercellular spaces are filled with strongly hydrophobic lamellar lipids, the product of membrane-coating granules. The combination of hydrophilic cornified cells in hydrophobic intercellular material is a barrier to both hydrophilic and hydrophobic substances (Ebling, 1993). Thickened epidermis also may diminish the concentration of pharmacological agents in the dermis.

**Parameters Controlling Absorption.** The absorption of drug into the skin is a function of the nature of the drug, the behavior of the vehicle, and the status of the skin. Three major variables account for differences in the rate of absorption or flux of different topical drugs or of the same drug in different vehicles: the concentration of drug in the vehicle, the partition coefficient of drug between the stratum corneum and the vehicle, and the diffusion coefficient of drug in the stratum corneum.

The rate of diffusion is proportional to the concentration of drug in the vehicle. The relationship is linear only at low drug concentrations and only applies to soluble drug in the vehicle. The latter factor may explain the variable therapeutic effects of different formulations of the same drug. The partition coefficient is a measure of the drug's ability to escape from the vehicle and is defined as the equilibrium solubility of drug in the surface of the stratum corneum relative to its solubility in the vehicle. Increased lipid solubility favors penetration of drugs through the skin by increasing the solubility in the relatively lipophilic stratum corneum. The diffusion coefficient indicates the extent to which the matrix of the barrier restricts the

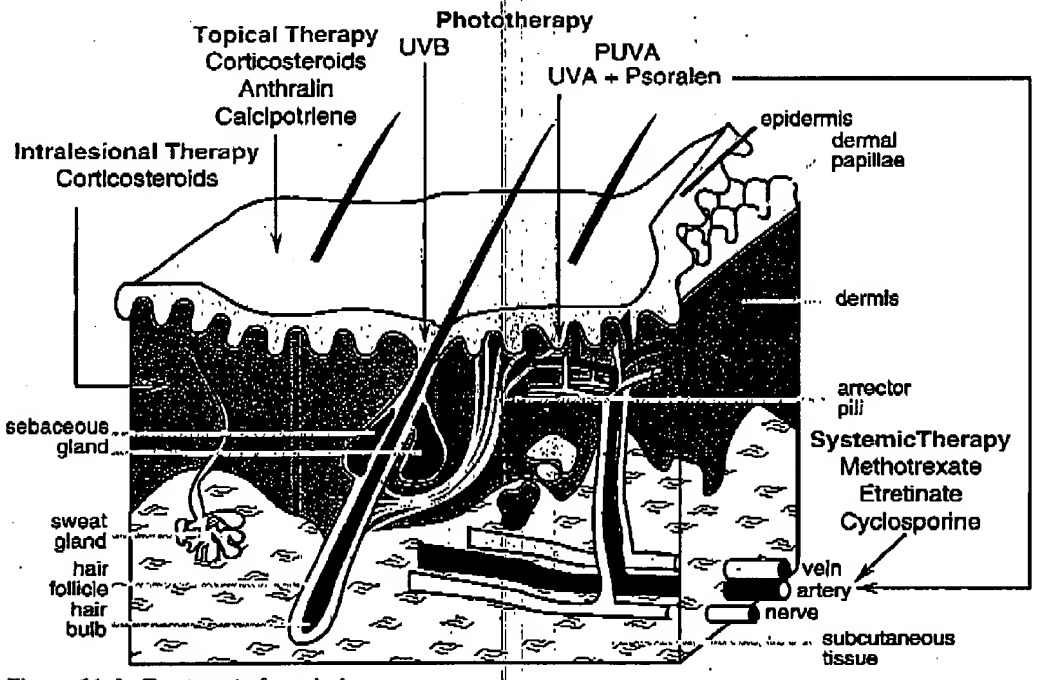


*Figure 64–1. Treatment of psoriasis.*

In psoriasis, a hyperproliferative disease, all four modes of therapeutic delivery are used: topical therapy, phototherapy, intralesional therapy, and systemic therapy. Major normal cutaneous structures are shown. PUVA, psoralen and ultraviolet A; UVB, ultraviolet B.

mobility of the drug. Increases in the molecular size of the drug will increase frictional resistance and decrease the diffusion coefficient (Franz, 1983); molecules over 1000 daltons usually will not be absorbed easily into normal adult skin.

Finally, intact stratum corneum is an excellent barrier, but in disease states the resistance to absorption is rapidly lost and absorption can be facilitated.

**General Guidelines for Topical Therapy.** ***Dosage.*** An amount of topical medication sufficient to cover affected body surfaces in repeated applications must be dispensed to the patient. A general rule is that approximately 30 g is required to cover the entire adult body once. Cost and inconvenience may prohibit the use of topical therapy repeatedly over large surface areas.

***Regional Anatomic Variation.*** Permeability is generally inversely proportional to the thickness of the stratum corneum. However, in certain areas, differences in lipid concentration may affect percutaneous absorption, depending on an individual drug's lipophilicity or hydrophilicity. Drug penetration is higher on the face, in intertriginous areas, and especially in the perineum. Consequently, sensitization, irritation, and atrophy from steroids are more likely to develop in these regions.

***Altered Barrier Function.*** In many dermatological diseases, such as psoriasis, the stratum corneum is abnormal, and barrier function is lost. Topical absorption is increased to the point that standard drug doses can result in systemic toxicity, for example, hypothalamic–pituitary–adrenal axis suppression from systemic absorption of potent topical steroids.

***Hydration.*** Drug absorption is increased with hydration, defined as an increase in the water content of the stratum corneum that is produced by inhibiting transepidermal loss of water. Methods of hydration include occlusion with an impermeable film, application of lipophilic occlusive vehicles such as ointments, and soaking dry skin before occlusion.

***Vehicle.*** Topical therapy is delivered by various vehicles, most frequently soaks, lotions, solutions, creams, and ointments, progressing in that order from least to most hydrating. The choice of vehicle may be as important as the active drug. In general, acute inflammation is treated with aqueous drying preparations, and chronic inflammation is treated with hydrating preparations. Soaks are the easiest method of drying acute moist eruptions. Lotions (powder in water suspension) and solutions (medications dissolved in a solvent) are ideal for hairy and intertriginous areas. Creams or oil-in-water emulsions are absorbable and are the most cosmetically acceptable to the patient. Ointments, water-in-oil emulsions, are the most effective hydrating agents, appropriate for dry scaly eruptions, but are greasy and therefore often undesirable. Multiple creams and ointments, without active drug, are marketed as moisturizing agents.

***Age.*** Children have a greater ratio of surface area to mass than adults, and a given amount of topical drug results in a greater systemic dose. The permeability of children's skin is increased in preterm infants (Barker *et al.*, 1987).

***Application Frequency.*** Topical agents are often applied twice daily. However, for certain drugs, once-daily application of a larger dose may be as effective as more frequent application of smaller doses. The stratum corneum may act as a reservoir and allow gradual penetration of a drug into the viable skin layers over a prolonged period of time. Intermittent pulse therapy—treatment for several days or weeks alternating with treatment-free time—may prevent development of tachyphylaxis associated with topical steroids.

## GLUCOCORTICOIDS

Glucocorticoids are frequently prescribed for their immunosuppressive and antiinflammatory properties. They are administered locally, through topical and intralesional routes, and systemically, through intramuscular, intravenous, and oral routes.

Mechanisms of glucocorticoid action are numerous, as discussed in Chapter 59. These include inhibitory effects on the arachidonic acid cascade, depression of production of many cytokines, and effects on inflammatory cells.

### Topical Glucocorticosteroids

Shortly after the synthesis of hydrocortisone in 1951, topical steroids were recognized as effective agents for the treatment of skin disease (Sulzberger and Witten, 1952). New halogenated glucocorticoids with greatly enhanced potency were synthesized in the mid-1950s, With the development of appropriate vehicles, these agents rapidly became the mainstay of therapy for many inflammatory skin diseases.

Topical glucocorticoids have been grouped into seven classes in order of decreasing potency (Table 64–1). Potency is measured using a vasoconstrictor assay, in which an agent is applied to skin under occlusion and the area of skin blanching assessed, and the psoriasis bioassay, in which the effect of steroid on psoriatic lesions is quantified (McKenzie and Stoughton, 1962; Dumas and Scholtz, 1972). Other assays of steroid potency involve suppression of erythema and edema following experimentally induced inflammation.